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MCKEE, VOORHEES & SEASE, P.L.C.
801 GRAND AVENUE
SUITE 3200
DES MOINES, IA 50309-2721

| EXAMINER |
|---|
| FREDMAN, JEFFREY NORMAN |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 07/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/900,063 | ROTHSCHILD ET AL. | |
| | Examin r | Art Unit | |
| | Jeffrey Fredman | 1634 | |

*-- The MAILING DATE of this communication app ars on the cover sh t with th correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *4-6,12,13,15,21-25,30-35,39,42-44,46-48 and 50-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-11,14,16-20,26-29,36-38 and 40, 41, 45, 49, 54, 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## DETAILED ACTION

### *Election/Restrictions*

1. New claims 42-44, 46-48, 50-53 are drawn to nonelected groups or species and are withdrawn.

### *Sequence Rules*

2. The current case continues to fail to meet sequence rules outlined in 37 C.F.R. 1.821-1.825. In particular, while the corrections to the specification are noted, the CRF was not accepted by STIC. Please find attached a copy of the Raw Sequence Listing Error Report generated by STIC regarding the computer readable form.

### *Specification*

3. The objection is withdrawn in view of the amendment.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38, 40, 41, 45, 49, 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding

genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which comprise prolactin receptor polymorphisms which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named four polymorphisms for which data is provided demonstrating an association with the phenotypic trait, litter size. Thus, applicant has express possession of only four particular polymorphisms, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. Even in the narrower dependent claims, such as claim 7, where MseI is required, no specific polymorphism is named. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with litter size is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing

additional sequence, which are associated with any phenotype are described in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition in claim 1 of a polymorphism associated with litter size which lacks any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the four specific polymorphisms, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a polymorphism in the prolactin receptor gene", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred,

> that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise prolactin receptor polymorphisms. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

***Response to Arguments – Written Description***

6. Applicant's arguments filed June 4, 2003 have been fully considered but they are not persuasive.

Applicant argues that the claims now comply with the written description requirement because they include SEQ ID NO: 3 in claim 1. This argument is not persuasive because the claim still reads "95 % sequence identity" as well as "fragment thereof". Applicant is not in possession of any additional sequence embodied by the 95% sequence identity or fragment language. Also, a significant number of claims,

including claims 40 and 54, lack any structure whatsoever. There is no definition of other animals or other useful polymorphisms by structure in this broad claim. Applicant is trying to capture polymorphisms which are not described and which are not currently known (and therefore to which Applicant does not have possession), by using broad fragment and percent identity language. This is precisely the problem identified by the court in Lilly, which noted "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Here, there may very well be 95% identical sequences to SEQ ID NO: 3 which have polymorphisms that are associated with litter size, but Applicant is not in possession of these sequences.

Applicant then argues that selection of additional restriction enzymes would be routine in the art. This argument is an enablement argument. The issue for written description is not whether the selection is routine, but whether Applicant had possession. To the extent that claim 40 is now a generic claim, it will be addressed by prior art. Applicant argues limitations with regard to SEQ ID NO: 3, but these limitations are not found in claim 40.

Applicant finally argues that naming the restriction enzyme names the polymorphism. The dependent claim still reads upon any sequence that is 95% identical or a fragment based upon the independent claim. Therefore, the dependent MseI claim also remains rejected.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38, 40, 41, 45, 49, 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some polymorphisms in the porcine prolactin receptor such as the Alu polymorphism, does not reasonably provide enablement for all polymorphisms including the MseI polymorphism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of screening animals for polymorphisms in the prolactin receptor gene which are associated with increased litter size. The invention is is the class of invention which the CAFC has characterized as "the unpredictable arts

such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass a method of screening for any polymorphism in the prolactin receptor gene. In fact, claim 40 as amended is now open to screening for any polymorpism in any gene whatsoever, in any species. Even the narrow claim 7 is drawn to any polymorphism which can be detected by the use of the MseI restriction enzyme. The method broadly encompasses the use of the method in any type of mammalian patient. This means that the method is broadly drawn to the use, not only of pigs, but also of sheep, bats, whales or any other mammal. Further, the animals undergoing the screening may contain any of a number of complicating variables, since the background genotype with regard to other genes may play significant roles in the effect on litter sizes.

Quantity of Experimenation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as litter size. Screening each possible polymorphism in the prolactin receptor gene represents an inventive, unpredictable and difficult undertaking in itself. As shown in the results on page 46, over 1500 litters were analyzed involving literally hundreds of pigs. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The specification demonstrates the unpredictability of this invention, since the P values identified by the specification for the association of the MseI SNP with litter size are 0.2 and 0.3. As Thisted et al notes (See http://www.stat.uchicago.edu/~thisted) "It has become scientific convention to say that p-values exceeding 0.05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5)". Thus, by scientific convention, the data presented for the Mse1 SNP on page 46 of the specification fails to demonstrate a statistically significant effect. It is highly unpredictable whether the SNP is, in fact, associated with the increased litter size. Unlike the Alu1 polymorphism, shown on page 36, where there is a P value below 0.05, the Mse1 polymorphism fails to show a significant effect. The factor of unpredictability weighs against the enablement of the claims.

Working Examples

The specification has a working example where an Alu polymorphism is clearly associated with litter size.

Guidance in the Specification.

The specification, while suggesting an association between the MseI SNP and litter size, did not provide sufficience evidence to demonstrate the association.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching that the P values are insufficient are opposed to enablement of the invention (see Thisted above). The specification provides one with no written description or guidance that leads one to a reliable method where an MseI polymorphism is associated with litter size. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms as prognostic of litter size as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the specific polymorphism at issue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Response to Arguments - Enablement***

8. Applicant's arguments filed June 4, 2003 have been fully considered but they are not persuasive.

Applicant argues that the claims are limited to animals which have 95% sequence identity to SEQ ID NO: 3 or a fragment thereof. First, claim 40 was amended to remove sequence restrictions, so any arguments relying upon the sequence do not address all the claims. Second, the use of the "fragment" language give immense

breadth, since every sequence in the world comprises one of an "A", "G", "C" or "T" fragment of SEQ ID NO: 3. Thus, not only is claim 40 currently broad enough to read on other genes besides prolactin, but even claim 1 can read on other genes.

Applicant then argues selection of variants is routine. This is not correct because it is entirely unpredictable if there are variants. In fact, Applicant is attempting to claim this subject matter because it is not routine. It is entirely unpredictable and inventive whether any particular polymorphism is associated with litter size. In particular, this unpredictability, combined with the other factors, supports a conclusion of undue experimentation. Unlike the simple screening assay in Wands itself, where experimental success was assured so long as sufficient resources were expended, since eventually an antibody producing cell would be isolated, here there is no assurance or even likelihood of success, since there is no reason to believe that other polymorphisms necessarily exist which have the desired correlation. At the time of the invention, it is speculative and without evidentiary basis to predict if there will be any results from the screening for additional polymorphisms, unlike Wands where it is not only possible but expected that results will be achieved. Here, there is no expectation that other polymorphisms associated with litter size will be found.

Applicant's traverse the argument that the P value is not statistically significant. Whether Applicant traverses it or not, the data in the specification lacks a P value that is high enough to be significant. Contrary to Applicant's statement, either the MseI allele is or is not associated with litter size. The statistical evidence of the specification

suggests it is not associated, in a significant way, with litter size. This supports the unpredictability argument and the enablement rejection.

Applicant argues that there is sufficient guidance in the specification. No such guidance is found because there is no evidence that the MseI allele is associated with litter size from the specification. This would not be useful under 35 U.S.C. 112, first paragraph and the rejection is maintained.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 40 is rejected under 35 U.S.C. 102(b) as being anticipated by Rothschild et al (U.S. Patent 5,374,526).

Rothschild teaches a method of screening animals to determine those more likely to produce larger litters (abstract) comprising:

(a) obtaining a biological sample from said animal (see column 4, lines 46-53),

(b) assaying for the presence of a genotype in said animal which is associated with increased litter size (see column 4, lines 13-34), said genotype characterized by a restriction fragment pattern said patterns when compared to a second restriction pattern is known to have or not have a desired marker (see column 6, line 62 to column7, line 2) wherein the presence of said marker is indicative of an animal more likely to produce larger litters (see column 6, line 62 to column7, line 2).

***Double Patenting***

11. The rejection of claims under the judicially created doctrine of obviousness-type double patenting is withdrawn in view of the terminal disclaimer.

***Conclusion***

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers

for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

July 22, 2003